The Properties and Regulation of Prostatic Stem Cells and Their Relevance to Prostatic Diseases

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Stem cell biology and tumorigenesis may be closely linked and prostatic stem cells may have a role in the etiology of cancer. Stem cells and tumor cells have many common features including self-renewal, multi-drug resistance, telomerase expression, and, in the case of the prostate, androgen independence. As prostatic carcinoma usually progresses to an androgen-independent tumor (which may reflect a stem cell-like phenotype), an understanding of prostate stem cell biology is important for devising preventative or therapeutic approaches for prostate cancer. In addition to being a source of carcinomas, stem cells may also give rise to benign prostatic hyperplasia.

We find that the proximal region of mouse prostatic ducts is enriched in a subpopulation of cells that are slow cycling and have a high proliferative potential. Cells from proximal and distal regions of prostatic ducts were combined with urogenital sinus mesencyme (UGM) and implanted under the renal capsule (RC) to determine the relative growth potential of proximal versus distal cells. Proximal cells form significantly more (312 ± 167 mg) prostatic tissue under the RC than distal cells (20 ± 19 mg). Proximal prostate cells could be passaged four times *in vivo* compared with two times for distal cells. They also survived prolonged periods of androgen ablation. The proximal stem cells can be purified from the proximal region by virtue of their high expression of the Sca-1 surface antigen. Sca-1 expressing cells from the proximal region are much more effective in generating prostatic tissue *in vivo* than a comparable population of Sca-1 depleted cells (203 ± 83 mg versus 12 ± 9 mg).

We determined the mechanism by which proximal stem cells are maintained in a quiescent state. We show that proximal cells isolated from an intact prostate produce significantly more active TGF-β than distal cells (19.7 ± 3.5 versus 2.3 ± 1.2 pg TGF-β/10^3cells respectively). In addition we find that the proximal region responds differently to TGF-β than the distal ductal region, and that under physiological conditions, androgens and TGF-β are crucial overall regulators of prostatic tissue homeostasis. We

find that high levels of TGF-β signaling are present in the quiescent proximal region in an androgen replete animal and that cells in this region over express Bcl-2 which protects them from apoptosis. Moreover, androgen ablation reverses the proximal-distal TGF-β signaling gradient, leading to an increase in TGF-β signaling in the unprotected distal region (low Bcl-2 expression). This reversal of TGF-β-mediated signaling accompanies apoptosis of cells in the distal region and gland involution after androgen withdrawal. A physiological TGF-β signaling gradient (high proximally, low distally) and its functional correlates are restored following androgen replenishment. In addition to highlighting the regulatory role of androgens and TGF-β, these findings may have important implications for the deregulation of the stem cell compartment in the etiology of proliferative prostatic diseases.